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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,791	01/08/2005	Alexander Domling	62660(52171)	3248

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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,791	DOMLING ET AL.	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-22* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10, 12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In many of applicant's correspondence the application number shown is 10/520,**719**, which is wrong. The correct application number is 10/520,791.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/30/06 has been entered.

Claims 7-22 are pending.

Claim 11 have been withdrawn from further consideration as being drawn to non-elected species.

Claims 7-10 and 12-22 are examined on the merit.

Addition of new claims 21 and 22 are acknowledged.

Claims 1-6 have been canceled.

Any objections and rejections not specifically mentioned here is considered withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-10, 14, 15 and 20-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sasse, et al., The Journal of Antibiotics, 2000, 53, 879-885, in view of Greenwald, Journal of Controlled Release, 2001, 74, 159-171 as stated for claims 7-10 and 12-17 in the office action dated 1/23/06.

Applicants have pointed out (for the second time in their remarks, see the earlier remark dated 4/34/06, page 6) that that the Greenwald reference teaches conjugates of drugs with higher molecular weight PEG (>20,000d). Applicants state that the argument is moot in light of the aforementioned response to arguments. Because, the applicant uses the synthetic methods described in the Greenwald reference to synthesize their tubulysin conjugates.

Applicants also point out again that Greenwald reference do not disclose any type of PEG conjugates of tubulysin compounds and the primary citation of Sasse, et al., do not disclose conjugates of any type.

Applicants further make the following comment, "Moreover, the reference in Applicant's application to Greenwald, Bioorg. Med. Chem. 1998, 6, 551-562 does not somehow that Greenwald, Journal of Controlled Release, 2001, 74, 159-171 is a legitimate citation in the present rejection". They continue their argument and state that applicant's own disclosure cannot be relied upon to substantiate a rejection under 103.

Applicant states that the 132 declaration submitted details data of enhanced results relative to non-conjugated tubulysin compounds.

Applicant's arguments filed 11/30/06 have been fully considered but they are not persuasive. The reference of Greenwald teaches the PEG (>20,000d) conjugates of drugs and the motivation for pegylating a drug molecule is to increase the half-life of the drug in vivo and to increase solubility of the drug as mentioned in the office action dated 1/23/06 (page 3).

Applicant's comment that, 'An Applicant's own disclosure can not be relied upon to substantiate a rejection under Section 103' is not persuasive. It is unclear, as what part of the disclosure that cannot be relied upon with respect to prior art of Greenwald that Examiner cannot rely upon. The cited references of Greenwald are legitimate prior art references to the instantly claimed invention and hence can be utilized to reject claims under obviousness statute.

With regards to the applicants argument that Greenwald do not disclose, teach or suggest tubulysin-PEG conjugates, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where

there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Greenwald teaches the PEGylation of drugs with PEG (>20,000d) to increase the half-life of the dugs in vivo and increase the solubility of the drug. Applicants have shown in their Rule 132 declaration that the pegylation of tubulysin enhanced the solubility by 10-40 fold in phosphate buffer. The cited prior art of Greenwald shows that the solubility of anticancer drug campothecin (CPT) increased to 2 mg/ml from 0.0025 mg/mL which is ~800 fold. Therefore, the result obtained by applicants is not unexpected over the prior art. Applicants have also shown the efficacy of the Peglated tubulysin in two cancer cell lines. However, the study does not include comparison to another anticancer drug. Therefore, it would be obvious to pegylate the tubulysin as the pegylation increases the solubility, enhances half life and suppresses the immunogenecity of the drug as shown by the prior art. Therefore the obviousness rejection as stated is proper and maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 13, 16-19 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as stated for claims 7-10 and 12-17 in the office action dated 1/23/06.

Applicants allege that no evidence has been cited to substantiate why the present case may be non-enabling. Applicants state that tubulysin compounds are disclosed at page 1 of the application. Linkers and polymers are disclosed in detail at page 7. At pages 11 and 12 of the application, specific examples are detailed. Therapeutic uses of compounds of are detailed for instance at page 10 of the application. At page 1 of the application, therapeutic activity of tubulysin compounds are disclosed. Based on such extensive disclosure the skilled worker would have been able to make the compound of the invention.

Additionally, applicants have presented a Rule 132 declaration from Alexander Domling demonstrating the anticancer activity of applicant's compounds.

Applicant's arguments filed 11/30/06 have been fully considered but they are not persuasive. Because, applicants claim innumerable compounds represented by the formula of claim 7. As stated in office action dated 1/23/06, the disclosure is inadequate because, in the absence of a synthetic schemes to synthesize the instantly claimed innumerable compounds, one skilled in the art would not be able predict which compounds of formula 1 are isolated from which microorganism. The unpredictability in the art is also very high as shown in the primary reference of Sasse, et al., (see page 6 of office action dated 1/23/06). The specification has disclosed making three variants of tubulysin A conjugated to PEG and is silent on how myriads of different compounds of 'U' represented by formula 1 are either isolated from microorganisms or synthesized via chemical synthesis. The disclosure is also silent on how any of these innumerable compounds are tested for biological activity for their anticancer properties.

The Rule 132 declaration filed on 11/30/06 substantiates the motivation for modifying the tubulysin compounds by conjugating to PEG as stated in the office action dated 1/23/06. The declaration compares the solubility of the unmodified tubulysin with the pegylated tubulysin showing that pegylation improved the solubility of the tubulysin, and the higher molecular weight of the PEG used for the conjugation augmented the solubility of the compound in sodium phosphate buffer. Applicants have shown in their Rule 132 declaration that the pegylation of tubulysin enhanced the solubility by 10-40 fold in phosphate buffer. The cited prior art of Greenwald shows that the solubility of anticancer drug campothecin (CPT) increased to 2 mg/ml from 0.0025 mg/mL which is ~800 fold. Therefore, the result obtained by applicants is not unexpected over the prior art. With regard to activity of the pegylated compounds shown in the 132 declaration applicants compared the activity of the pegylated tubulysin in two different cancer cell lines and no data was available (in the 132 declaration) comparing the activity of the pegylated tubulysin to another anticancer drug thereby showing that the compounds of instant application has unexpected activity (properties) compared to other anti cancer agents and non-pegylated tubulysin. Therefore, the results of the declaration would be expected. Therefore, the rejection under 35 USC 112 first paragraph for lacking enablement is proper and is maintained.

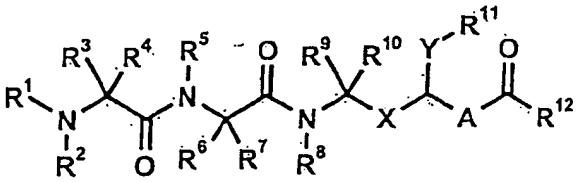
New grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 and 12-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant application, applicants claim a compound of general formula U-V-W wherein 'U' refers to formula I as shown below,



(I)

wherein

A is an optionally substituted 5- or 6-membered heteroarylen ring;

X is an oxygen atom, a sulfur atom, or a group of the formula NR13 or $CR^{14}R^{15}$;

Y is an oxygen atom, a sulfur atom or a group of the formula NR16,

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are independently of each other H, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or heteraaralkyl,

or two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} R12, R^{13}, R^{14}, R^{15} and R^{16} constitute part of a cycloalkyl or heterocycloalkyl ring system;

V is a linker and W is a polymer or a biomolecule.

Applicants also claim a method of treating a patient suffering from cancer comprising administering to the patient one or more compounds U-V-W.

The claims as recited represent innumerable compounds with variety of linker moieties conjugating to a polymer or a biomolecule. The claims as recited and disclosure in the specification are inadequate to describe the claimed invention of the instant application in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include, "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient" MPEP 2163.

In the instant application, claims are drawn to composition claims are drawn to a structure of the molecule U-V-W wherein the 'U' represents innumerable variations of formula I as shown above, 'V' represents number of linker moieties as recited in claim 14 and 'W' is a polymer or a biomolecule. The specification lists few of tubulysin compounds on page 1 as representatives of 'U', on page 7 linkers and polymers are disclosed as a list of compounds and on page 10 of the application applicants disclose therapeutic uses of compounds. The disclosure

also embodies three structural variants of tubulysin compounds conjugated to PEG on pages 11 and 12. As per the requirement of the written description criteria, the claims as recited and the disclosure in the specification is inadequate to describe the present invention that claims myriads of compounds of formula 1 along with variety of linker moieties conjugated to polymers or biomolecules. The specification is also inadequate in describing how the innumerable compounds represented by formula I are synthesized as the specification is silent on chemical synthesis of number of variants of 'U'. In the absence of a synthetic scheme to make these compounds, the specification is inadequate in describing the microbial source for isolating variety of structurally distinct compounds represented by formula I. The specification is inadequate with respect to written description requirement as to describe the nature of structure-function relationship of the compounds represented by formula I. The specification is also silent on how these compounds are screened for the desired biological activity.

Moreover, the structure as recited in claim 7 for formula I "or two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} constitute part of a cycloalkyl ring system" clearly indicate that if two of the R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} form a part of a cyclic structure, it will not form a cycloalkyl ring because of the presence of amide bonds in the backbone structure as recited in the claim.

The specification is also inadequate in terms describing the type of biomolecules used in the invention with specific examples to support the claims as recited. The only specific examples shown in the specification shows the structure of three variations of tubulysin molecules with PEG as the polymer.

The specification is inadequate in describing the application of the compounds of instant invention in methods of treating cancer as claimed by the applicants. The specification lacks examples showing efficacy of the innumerable compound claimed in the invention in treating patients suffering from cancer.

Therefore, the claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Objections

Claim 7 objected to because of the following informalities: The R^{11} and R12 are not separated by a ',' as required and in R12, the numbers are represented as superscript. Appropriate correction is required.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyanarayana R. Gudibande, Ph.D.
Art Unit 1654

1/30/09
ANISH GUPTA
PRIMARY EXAMINER